REMARKS

Claims 1-2 and 7-12 are pending in the application. Claims 1 and 10 are allowed. Claim 2, 11-12 and 20-28 are rejected. Claims 2, 11 and 12 have been amended. No new matter has been added.

In light of the claim amendments and the following remarks, Applicant respectfully requests that the Examiner withdraw the rejections and pass this case to issuance.

Priority

The Office Action states that application serial nos. 60/116,748, 60/127,142 and parent application no. 09/491,896 fail to provide an enabling disclosure for the invention claimed in claims 1, 2, 4-12 and 14. Applicant disagrees with this assessment, and submits that the priority documents do provide adequate support for the claims under 35 U.S.C. § 119(e) and 120. The Examiner is thanked for the acknowledgement on page 3 of the June 11, 2009 Office Action that "the priority issue stands or falls with the enablement rejection." Since *composition* claims 1-2 and 10 are now in condition for allowance, enablement is discussed below with regard to *method* claims 11-12 and 20-28.

Amendments to the Claims

Claim 2 has been amended to recite "NMDA-*1* receptor." The amendment is made to correct antecedency.

Claims 11 and 12 have been amended recite "*mammalian* subject." Support for the amendments can be found throughout the specification and in, for example, in paragrah [0070] of the published application. Claims 11 and 12 have also been amended to recite "prior to a neuronal insult" for clarity. Support for the amendments can be found in paragraph [0263] of the published application.

Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 2, 11-12 and 20-28 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification "does not reasonably provide enablement for a composition comprising any

vector encoding *any* NMDA receptor antigen, nor for a method of modulating or delaying onset of epilepsy, stroke, or decreased cognition in *any* subject, by administration of any vector encoding any NMDA receptor antigen." Each of these issues is discussed below.

"Any NMDA receptor antigen"

Amendments have addressed this issue by amending each of the independent and dependent claims to specify *an NMDA receptor-1 antigen*. Since the Examiner has already acknowledged (on page 4 of the December 10, 2009 Office Action) that the claims are enabled for the NMDAR-1 antigen, this ground for rejection is now moot.

"Any subject"

Since the composition claims 1-2 and 10 currently stand allowable, the scope of enablement is only pertinent to the pending method claims and Applicant again asserts that the specification which presents experimental results in specific animals is enabling for a broader scope of *mammalian* subjects as defined in the specification, including humans. Claims 11 and 12 have been amended to specify the subject is a *mammalian* subject.

The Office Action has cited the McCluskie article (McCluskie et al. (1999) Mol. Med. 5:287-300) as the principal basis for the enablement rejection, noting that:

> ...McCluskie et al. teaches that the strength and nature of the immune responses to administration of DNA vaccines varies between species and that it is not clear that the results from one species are predictive in another (page 287, abstract).[1]

The suggestion that McCluskie's article makes the results "unpredictable" is not supported by the article. McCluskie investigated humoral responses to genetic vaccines in mice and monkeys. McCluskie's experiments were designed such that a similar dosage was administered to the monkeys (1mg) and the mice (0.1mg), only a 10x difference in dosage while there is a 100x weight difference between the species. So it is not at all surprising that the mice demonstrated antibody formation (received 10 fold more DNA vaccine), while the monkeys demonstrated a poor antibody response.

[1] See page 4 of the December 10, 2009 Office Action.

Subsequent to McCluskie's article, several studies have demonstrated that efficacy of a DNA vaccine in an animal model is indeed predictable of efficacy in humans. See, for example, Li et al., Int. Immunol. (2005) 17:1293-1302 (Appendix A) describing a powder-injectable hepatitis B DNA vaccine (see Roy et al., Vaccine (2000) 19:764-778 abstract, Appendix B) that stimulated specific cellular immune responses in mice and vigorous T cell responses in human clinical trials. Moreover, Tollefsen et al. (Scan. J. Immunol. (2002) 57:229-238, Appendix C) showed antibody responses in rodents and large farm animals to DNA vaccination via electroporation. Therefore, Applicant asserts that experimental results in rodents is enabling for a broader scope of mammalian subjects as demonstrated by the prior art at the time of filing.

Furthermore, the Examiner is reminded of the standard stated in the MPEP 2164.02, "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." Thus, the experimental results demonstrated in the specification are in an art recognized model that correlates to a specific condition.

The Applicant has demonstrated the claimed invention in animal models accepted by those skilled in the art. In fact, following the filing of this application, Applicant's work was published in the peer-reviewed journal, *Science*, further demonstrating the animal models presented in the application were indeed accepted by those skilled in the art. See. During et al. "*An Oral Vaccine Against NMDAR1 with Efficacy in Experimental Stroke and Epilepsy*," Science Vol. 287 1453-1460 (February 25, 2000).

Therefore, one of ordinary skill in the art, with knowledge of the prior art, would be capable of administering a nucleic acid sequence antigen to a *mammalian subject* to produce antibodies in the circulatory system of a subject.

Mode of administration

While only presenting experimental results with an *oral composition*, the specification fully enables other modes of administration as well. See, for example, Section III ("Pharmaceutical Compositions and Pharmaceutical administration") – paragraphs [0120-0133] of the published application and Section IV ("Delivery Systems") – paragraphs [0134-0148] of

the published application, in which alternative delivery mechanisms such as intravenous and intramuscular injection are taught in detail.

Moreover, the references cited above (Li et al., Roy et al. and Tollefsen et al.) both use different routes of administration and obtain efficacy in rodents, larger mammals and humans regardless of administration route. The suggestion that McCluskie's article makes the claims "unpredictable" is not supported by the more recent art, since unlike McCluskie, varying modes of administration in a range of mammals have demonstrated antibody response to DNA vaccination.

Therefore, it is well within the capabilities of one of ordinary skill in the art, at the time of filing, to utilize the teachings of the specification to administer a nucleic acid sequence antigen, *via oral administration or the other recited modes*, to produce antibodies in the circulatory system of a mammalian subject.

Any vector

Amendments have addressed this issue by amending each of the independent claims that recite a vector to specify *an adeno-associated viral vector*. Since the Examiner has already acknowledged (on page 4 of the December 10, 2009 Office Action) that the claims are enabled for AAV vector, this ground for rejection is now moot.

In summary, the Examiner bears the burden of establishing a basis for questioning enablement. See MPEP 2164.04. Despite numerous office actions, a reasonable basis for rejecting the scope of Applicant's method claims, especially claim 12, has not been presented.

CONCLUSION

In view of the above remarks, Applicant' respectfully requests reconsideration and allowance of the application. The Examiner is invited to call the undersigned at (617) 439-2948 if there are any questions. In the event that the amendments do not place this case in condition for allowance, entry of the amendments and a further advisory action are requested to facilitate appeal.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 141449, under Order No. 106604-7.

Dated: June 10, 2010

Respectfully submitted,

By__/Thomas J. Engellenner/_____
Thomas J. Engellenner
Registration No.: 28,711
NUTTER MCCLENNEN & FISH LLP
World Trade Center West
155 Seaport Boulevard
Boston, Massachusetts 02210-2604
Phone: 617-439-2948
Fax: 617-310-9948
Attorney for Applicant

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